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Patentanmeldung Nr. Patent application No. Demande de brevet n°

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Pharmaceutical tablets containing tibolone

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Pharmaceutical tablets containing tibolone.

The invention relates to a pharmaceutical tablet comprising an amount of from 0.1 to 10 % by weight of tibolone.

Compositions comprising tibolone, the chemical name of which is (7α,17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one (also denoted as Org OD 14) and a pharmaceutically acceptable solid excipient have been described in EP 389 035. Tablets comprising tibolone are available in medical practice, for example, under the name of Livial®.

A known formulation for tibolone is a 100 mg tablet having 2.5 mg of tibolone contained therein, a relatively small amount (e.g. approximately 1 % by weight) of pharmaceutically acceptable auxiliaries, and an excipient making up the body of the tablet. The excipient of the body typically is composed of 10 % by weight of starch, e.g. potato starch, and 90 % by weight of lactose.

Upon long-term storage of tibolone containing products degradation products of tibolone appear. The major degradation product is (7α,17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one (Org OM38). Org OM38 differs from tibolone in that the double bond in the steroid skeleton is located between positions 4 and 5, whereas in tibolone it is located between positions 5 and 10. This isomeric degradation product is identifi[illegible]ity in tibolone containing tablets and limits the ap[illegible]ailable tablets to a maxim[illegible]elonging the sh[illegible]ses it is ad[illegible]g OM3[illegible]

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The [illegible]ng pro[illegible]g pro[illegible]rified tib[illegible]

EP

US

m[illegible] WO98/[illegible] life of tibolone tablets still need[illegible] at two years storage the levels of Org OM38 in some[illegible]s can

exceed 5% by weight with respect to the initial tibolone content. The present invention provides tibolone tablets with less Org OM38 formation and thus are an alternative or improvement over the tablets disclosed in WO98/47517.

It is found that a pharmaceutical tablet comprising an amount of from 0.1 to 10 % by weight of tibolone provided with a coating has a lower content of Org OM38 after long-term storage than a similar tablet without the coating. It is unexpected that a coating reduces the emergence of the isomerisation degradation product. There is no current explanation of the mechanism by which a coating prevents the formation of this isomerisation product.

A specific embodiment of the invention is formed by the selection of a coating out of the group formed by film coating, sugar coating and wrap coating according to US5146730. Another embodiment of the invention is a pharmaceutical tablet comprising an amount of from 0.1 to 10 % by weight of tibolone provided with, as coating, having as a main component of the coating a layer of a polyalcohol, a cellulose ether, gelatine, acrylic or vinyl. A particular embodiment of the invention is a tablet comprising an amount of from 0.1 to 10 % by weight of tibolone provided with, as a main component of the coating, a layer of a polyalcohol, a cellulose ether or gelatine. A more particular embodiment is the mentioned tablet provided with, as a main component of the coating, a layer of polyalcohol. A main component is making up at least 30% of the coating material.

A polyalcohol is, for example, a mono- or disaccharide, glucose, sorbitol, mannitol or xylitol.

A cellulose ether is, for example, hydroxypropylmethylcellulose or methylcellulose.

An acrylic is, for example, methacrylate or a methyl methacrylate copolymer.

A vinyl is, for example, polyvinyl alcohol.

Coating techniques have a long history and have acquired many elaborations over time (Gennaro *et al*, Remington; The Science and Practice of Pharmacy; 20th ed., Publisher: Lippincott Williams & Wilkins; Baltimore; USA; Chapter 46: Coating of pharmaceutical dosage forms). The coating for the tablets according to the invention can be applied by following such well-known technical procedures.

For sugar coatings a seal coating and a sub coating are often applied, but for the tablets according to the present invention these coatings are only optional additions underneath the sugar coat. In particular, the effect of reducing Org OM38 formation can also be observed in sugar coated tablets without sub coat.

A coating may have further additives in order to improve the quality of the coating. For example a plasticizer may be added. The plasticizer should, of course, be compatible with the other components of the coating, in particular with the polymer used, for example, in a film coating. Such plasticizers are well known, for example glycerine, propylene glycol, polyethylene glycol, triacetin, acetylated monoglyceride, a citrate ester or a phthalate ester. A particular embodiment of tablets according to the invention has glycerine, propylene glycol or a polyethylene glycol in a film coating.

The wrap coating according to the disclosure in US 5146730 is not described in Remington; The Science and Practice of Pharmacy (*op. cit.*). With this method the tablets are wrapped with elastic plastic self-adherent film. The coating is applied by feeding a tablet into a cavity formed between a pair of dies over two elastic self-adherent films. A tablet, which is enveloped in this manner between the films is finally coated by sealing the films to each other along the lines contiguous to the tablet. The details of this method are described in US 5146730.

Other excipients typically comprised by coatings are pigments and colouring agents but these are not essential for the present invention and therefore may be absent.

The examples further illustrate the working of the invention.

Examples

Tablets of 65 mg total weight, containing 1.25 mg tibolone, were prepared from purified tibolone. The latter was obtained according to the method described in WO00/23460.

A basic granulate, consisting of 10% potato starch and 90% lactose, was manufactured in a Fluid Bed Granulator, using a starch mucilage as binding liquid.

Uncoated tibolone tablets

65.2 mg tablets having the composition of 1.25 mg tibolone, 63.29 mg basic granulate, 0.13 mg ascorbylpalmitate and 0.33 mg magnesium stearate were prepared as follows:

Approximately 10% of the basic granulate was premixed with tibolone and ascorbylpalmitate. After screening the premix through a 250 µm sieve, the rest of the basic granulate was added and mixing was continued. Finally, magnesium stearate was admixed and the final mixture was tabletted to tablets with a diameter of 5 mm.

Film coating

Tablets prepared as described above were provided with a film-coat with the following composition: 0.75 mg hydroxypropyl cellulose E15, 0.15 mg polyethylene glycol 400, 0.11 mg titanium dioxide and 0.19 mg talc. An aqueous dispersion of the coating excipients was sprayed onto the tablets using standard film coating equipment (Accela Cota™) at a rotation speed of the coating pan of 12.5 rpm, an inlet temperature of approximately 60 °C and an airflow of approximately 300 m^3/hour.

Sugar coat I

A batch of approximately 16 kg of tablets film coated as described above (now having the function of a seal coat) was provided with a sugarcoat with the following composition per tablet:

The coat is having an inner layer of approximately 26 mg per tablet consisting of approximately 20% arabic gum and approximately 80% saccharose, and an outer layer having the composition as listed in table 1:

Table 1

Composition of the outer layer (sugar coat)

The amount of the components are provided in weight percentages of the total weight of the composition

Arabic gum	4.4
Saccharose	56.5
Calcium carbonate	8.7

Talc	13.9
Titanium dioxide	6.1
Polyethylene glycol	0.9
Glucose syrup	0.9
Glycerol 86.5%	0.12
China clay	8.7

For application of the coat, tablets were added to the sugar coat pan. The rotating pan had a diameter of about 0.7 m and a rotation speed of 42 rpm. Room conditions were 21 °C and 46 % relative humidity.
A 60.2 w/w % dispersion of the balanced components for the inner layer was manually added step by step. Subsequently, a total of a few hundred grams of a layering powder consisting of 64.3 % talc, 21.4% calcium carbonate, 7.1 % saccharose, and 7.1% titanium dioxide was added manually. Between the addition of subcoat and layering powder, the tablets were dried in open air without forced drying. After finalizing the inner layer (subcoat), the sugar coat dispersion (approximately 77% w/w) in water was added in a number of sequential steps and finally the batch of sugar coated tablets was dried.

Sugar coat II

A batch of 8 kg of tablets film coated as described above was provided with a sugarcoat without an inner layer as subcoat.
The sugar coat dispersion (approximately 77% w/w) in water was added in the rotating pan having a diameter of about 0.7 m and with a rotation speed of 42 rpm the coating was applied in various steps. Finally, the batch of sugarcoated tablets was dried.

Results

Tablets prepared and coated as described above were packed in open brown glass bottles and were subjected to the storage condition of 25 °C and 60% relative humidity (RH) or 40 °C and ambient relative humidity. After six months the percentage of the degradation product Org OM 38 was measured in the tablets.

	At 25 °C and 60% RH[1)]		At 40 °C and ambient RH	
	% OM38	SD[2)]	% OM38	SD[2)]
Uncoated tablets	2.83	0.015	6.53	0.015
Film-coated	2.45	0.03	4.83	0.09
Sugar coat I	2.32	0.02	3.19	0.04
Sugar coat II	2.39	0.01	3.44	0.05

1) RH is Relative Humidity of the environment.

2) SD is the standard deviation in the mean obtained from three measurements from pooled tablets of 10 tablets per pool.

5 The results show that the coating of the tablets results in a decrease in the formation of the degradation product Org OM38

Claims

1. A pharmaceutical tablet comprising an amount of from 0.1 to 10 % by weight of tibolone provided with a coating.

2. The pharmaceutical tablet according to claim 1, whereby the coating is film coating or sugar coating or wrap coating

3. The pharmaceutical tablet according to claim 1 or 2, whereby a main component of the coating is selected from the list consisting of a polyalcohol, a cellulose ether, gelatine, acrylic and vinyl.

4. The pharmaceutical tablet according to claim 3, whereby the main component of the coating is a polyalcohol or a cellulose ether or gelatine.

5. The pharmaceutical tablet according to claim 3, whereby the main component of the coating is a layer of a polyalcohol.

6. The pharmaceutical tablet according to any one of claim 1-5, whereby the coating comprises at least one of a plasticizer selected from the list consisting of glycerine, propylene glycol, polyethylene glycol, triacetin, acetylated monoglyceride, a citrate ester and a phthalate ester.

7. The pharmaceutical tablet according to claim 6, whereby the coating is film coating and the plasticizer is glycerine or propylene glycol or a polyethylene glycol.

Abstract

The invention provides a pharmaceutical tablet comprising an amount of from 0.1 to 10 % by weight of tibolone provided with a coating, among which in particular a film coating or sugar coating or wrap coating. Such tablets have lower isomerisation degradation product OM 38 after storage.

Pharmaceutical tablets containing tibolone.

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Upon long-term storage of tibolone containing products degradation products of tibolone appear. The major degradation product is (7α,17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one (Org OM38). Org OM38 differs from tibolone in that the double bond in the steroid skeleton is located between positions 4 and 5, whereas in tibolone it is located between positions 5 and 10. This isomeric degradation product is identified as the major impurity in tibolone containing tablets and limits the approved shelf-life claim of the presently available tablets to a maximum of two years. Considerable advantage is achieved in prolonging the shelf life of tibolone containing tablets. For this and other purposes it is advantageous to find means to reduce the rate of formation of Org OM38.

The problem of reducing Org OM 38 formation in tibolone containing products was earlier addressed at two stages of the manufacturing process of tibolone tablets, that is at the stage of production of purified tibolone (Kirchholtes and Sas, WO00/23460) and at the stage of manufacture of the pharmaceutical formulation (De Haan et al, WO98/47517). Despite these contributions to the art, the shelf life of tibolone tablets still needs to be improved, because sometimes at two years storage the levels of Org OM38 in some batches of tablets can